Peer Review
Experimental Toxicology Division
NHEERL

Susceptibility of the Developing Immune System to Environmental Chemicals

SUSCEPTIBILITY, ALLERGY & ASTHMA

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INTRODUCTION

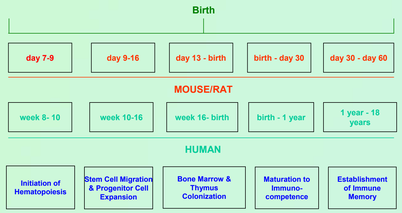
ISSUES:

- EPA is committed to promoting a safe and healthy environment for children through consideration of special childhood vulnerabilities to environmental agents.
- Windows of vulnerability exist during development, particularly during early gestation, but also throughout pregnancy, infancy, childhood, and adolescence.
- Children may also be more vulnerable than adults because of differences in absorption, metabolism, storage, and excretion, resulting in higher biologically-effective doses to target tissues.
- EPA has the mandate to implement legislation and policy on children's environmental health through the Food Quality Protection Act of 1996 (FQPA) and the Safe Drinking Water Act (SDWA) Amendments of 1996.
- Immunotoxicity research has focused primarily on adult animal exposure, while there are only a limited number of chemicals that have been examined for developmental immunotoxicity.
- Risk assessments based solely on adult immunotoxicity data is unlikely to result in effective protection of the potentially most at-risk populations.

GOALS:

- Determine the utility of a rodent model for the detection of potential increased immune dysfunction in young adult rats following environmental chemical exposure during immune system development.
- Identify possible "critical window(s)" of chemical exposure during immune system development by dosing in utero, perinatally (i.e., in utero to pre-weaning) and post weaning to pre-puberty.
- Determine if the developing immune system of the rat is more sensitive to chemical-induced immunosuppression compared to the adult rat.

CRITICAL WINDOWS OF EXPOSURE FOR THE IMMUNE SYSTEM



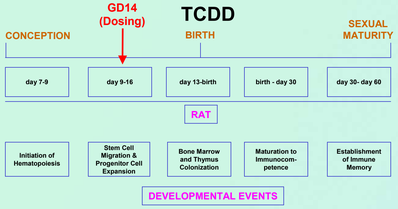
There are discrete windows of immune development where differential immunotoxic risk is likely to exist and through which comparative assessment between humans and rodents can be pursued (Dietert et al., 2000).

METHODS

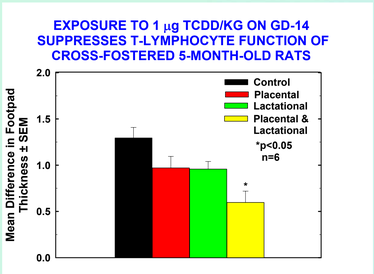
- Time-bred female Fischer 344 or Sprague Dawley rats, and/or their offspring, were dosed by gavage with 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD), methoxychlor (MXC) or heptachlor (H)
- Immune system function was assessed at puberty and in some instances at several months of age
- Immune function assays included the following:
  - lymphoid organ weights and cellularity
  - splenic NK cell activity and lymphocyte mitogen and MLR responses
  - flowcytometric lymphocyte phenotype analysis
  - antibody response to sheep red blood cells (SRBCs)
  - DTH & CHS responses to bovine serum albumin (BSA) and 2,4-dinitrofluorobenzene (DNFB) respectively
  - splenic and lymph node Th_1 and Th_2 cytokine profiles using real-time RT-PCR or the ribonuclease protection assay (RPA)

RESULTS

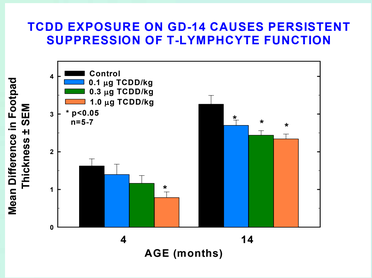
CRITICAL WINDOWS OF VULNERABILITY IN DEVELOPMENT OF THE RODENT IMMUNE SYSTEM



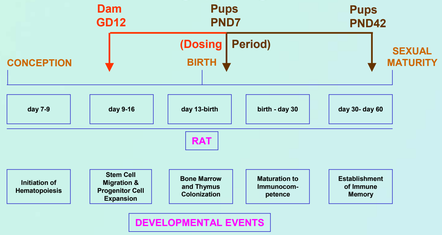
EXPOSURE TO 1 μg TCDD/KG ON GD-14 SUPPRESSES T-LYMPHOCYTE FUNCTION OF CROSS-FOSTERED 5-MONTH-OLD RATS



TCDD EXPOSURE ON GD-14 CAUSES PERSISTENT SUPPRESSION OF T-LYMPHCYTE FUNCTION

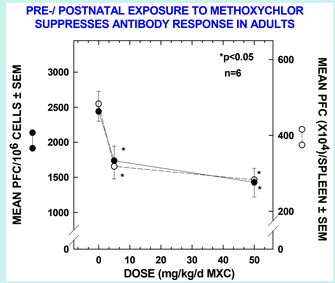


PESTICIDES



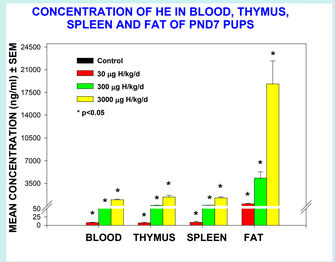
METHOXYCHLOR

PRE-/ POSTNATAL EXPOSURE TO METHOXYCHLOR SUPPRESSES ANTIBODY RESPONSE IN ADULTS



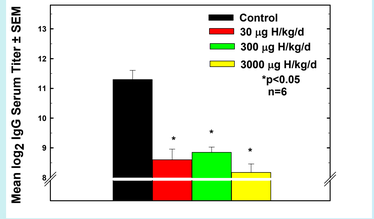
HEPTACHLOR

CONCENTRATION OF HE IN BLOOD, THYMUS, SPLEEN AND FAT OF PND7 PUPS



HEPTACHLOR

PERSISTENT EFFECT OF PERINATAL/JUVENILE HEPTACHLOR EXPOSURE ON IgG ANTIBODY RESPONSE TO SRBCs IN 26-WEEK-OLD RATS



CONCLUSIONS & IMPACT

- Exposure to TCDD, MXC or H, during immune system development results in "persistent" suppression of T cell-mediated immune responses.
- Exposure of adult rats at comparable doses of TCDD fails to alter immune function.
- Male offspring appeared to be more sensitive than females to chemical-induced developmental immunotoxicity.
- The amount of the metabolite H epoxide (HE) found in lymphoid tissue, following gestational and early lactational exposure to H, was inversely proportional to immune suppression. Comparable results occurred with MXC.
- The "critical window(s)" for immune dysfunction following developmental exposure to MXC and H was not determined, since exposure encompassed the entire period of immune system development in the rat.
- The results demonstrate "persistent" immune suppression in adult rats exposed during development, thereby identifying the need for further work in developmental immunotoxicology to assist EPA's efforts in children's risk assessment.

FUTURE DIRECTIONS

- Identification of the "critical window (s)" of developmental immunotoxicants (i.e., heptachlor, methoxychlor, and dexamethasone).
- Comparison of immune function alterations consequent to developmental exposure versus adult exposure.
- Detection of cellular and molecular targets associated with developmental immunotoxicity.
- Determine if the developing immune system is in fact more sensitive than the mature immune system to chemical- induced immunosuppression.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SOLVING AGENCY PROBLEMS